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PUSHING BOUNDARIES

CLINICAL TRIALS EXPLORE THE FRONTIERS OF MEDICAL SCIENCE – WITH THE HELP OF COURAGEOUS PATIENTS

In 1796, when Edward Jenner wanted to see if vaccinating people with cowpox would protect them from being infected with smallpox, all he had to do was convince a local farmer to volunteer his son for the experiment. Fortunately for the boy — and for countless individuals after him — the vaccine worked.

Clinical research has come a long way in the 200 years since that time. Before today's investigators even think about recruiting patients, they pass through a gauntlet of federal and institutional rules, regulations and procedures — all designed to protect human research subjects and reduce, as much as possible, the risks of participating in the study.

But some things haven't changed since Jenner's famous experiment. Without people willing to volunteer as research subjects, and without physicians willing to push the boundaries of established treatments, advances in medicine would not be possible.

This is the story of three of those physicians — Maha Hussain, Elizabeth Young and Nancy Barbas. Like many other physician-scientists in the U-M Medical School, they focus on clinical research with human subjects. Someday, Hussain's efforts may lead to more effective treatments for advanced prostate cancer. Young's work will give physicians guidance on how to treat their depressed patients more effectively. And Barbas' studies could help bring new drugs to fight the mental deterioration of Alzheimer's disease.

This is also the story of millions of people who volunteer for clinical trials and other research studies — at U-M and other institutions. Their quiet courage and their dedication to advancing the frontiers of medical science isn't the stuff of front-page news stories. But many medical breakthroughs would not happen without them. ➤

The person who invented the term "multi-tasking" must have known Maha Hussain, M.D., an oncologist who specializes in genitourinary cancer. An intense, dynamic woman and a native of Iraq, she received her M.D. from the University of Baghdad Medical School, and speaks in the cadences of her native Arabic.

Today, Hussain is eating lunch in a staff room at the U-M Comprehensive Cancer Center in the midst of her eight-hour clinic day while she scans pages of information flashing across a computer screen and discusses a patient's case with Samir Desai, M.D., an oncology resident. They are deciding whether the 77-year-old woman with advanced bladder cancer waiting in exam room 56 meets the criteria for a clinical trial of a new three-drug-combination therapy.

Once she confirms that the patient is eligible for the study, Hussain prints a copy of the consent document — an explanation of the study's procedures and risks written in plain English — which the patient must sign before she can be enrolled in the clinical trial.

After introducing herself and shaking hands, Hussain sits down and focuses all her attention on the patient as she explains the major points in the consent document: How standard therapy differs from the experimental treatment the patient will receive, if she agrees to enroll in the study. The risks of being in the study and the side effects she may experience from the drugs. How she is free to withdraw from the study at any time. How no one knows whether the experimental treatment will help her live longer than the standard therapy.

"Do you have any questions?" Hussain asks gently. Struggling to absorb everything she's just heard, the patient says no. Reassuring her that "Dr. Desai will go over all of this with you again," Hussain hands the patient her card and encourages her to read the consent document at home, and to call if she has questions.

Hussain is a clinical professor of internal medicine and oncology. She was recruited to U-M two years ago to expand the cancer center's clinical research program. Although the extra procedures, tests, paperwork and follow-up involved make it more time-consuming to treat patients in a clinical trial, Hussain sees it as a worthwhile investment — one that helps patients, as well as advances clinical care in line with the medical school's reputation as a major research institution.

"Our primary objective is to develop the most outstanding clinical care for our patients," says Hussain. "Often, the best clinical care for the seriously ill can be found in a clinical trial. There are no cures for the majority of advanced genitourinary cancers. So we try, as much as possible, to get our patients into appropriate clinical research studies."

Hussain has a national reputation in the field of cancer research. She advises the Food and Drug Administration on whether new cancer drugs should be approved for patient use, and also chairs the prostate cancer sub-committee of the Southwest Oncology Group, a cooperative organization of medical schools, cancer centers and hospitals, funded by the National Cancer Institute, that develops and conducts clinical trials of experimental cancer treatments.

Traditional chemotherapy works by poisoning cancer cells, but new anti-cancer agents attack cancer in different ways. Hussain is the principal investigator for several U-M clinical trials of experimental chemotherapy agents. One is a drug called Epithilone-B, which seems to prevent cancer cells from dividing and multiplying. Hussain says it could hold promise for men with advanced, metastatic prostate cancer who don't respond to standard treatment.

Hussain also is leading an NCI-sponsored trial of an investigational drug called EMD121974, which may inhibit the development of blood vessels tumors need to survive and spread. This study will enroll more than 100 prostate cancer patients from four different cancer centers in the U.S.

Managing a clinical trial with over a hundred patients in several sites is a major administrative challenge. "It's impossible to do this by yourself," Hussain says. "We need a team to assist us and ensure that we are conducting the trial appropriately with every attention to detail." So, in addition to staff in the Cancer Center's clinical trials office, Hussain will rely on the U-M Health System's Center for the Advancement of Clinical Research (CACR) to help her manage the study.

Funded by the U-M Health System and Medical School, CACR was created to provide administrative and technical support to help U-M faculty conduct large, multi-site clinical research studies.

"National multi-center trials are the ones most likely to be published in major medical journals and most likely to influence medical practice," says Daniel J. Clauw, M.D., CACR's director and a professor of internal medicine in the medical school. "U-M physicians should be doing the research that is asking and answering the most important questions in clinical medicine."

Fifteen years ago, when Hussain finished her oncology fellowship, there were few options for men with prostate cancer. "Other than hormone therapy, we didn't know of anything that worked," she says. "But an incredible amount of knowledge has been gained since then.

"We're in this business to make the future better for our patients. Everything we do adds a small step forward to hopefully solving the problem of cancer."

—Maha Hussain

In the last 10 years, two new drugs were approved by the FDA, and many others are under investigation. Now patients with end-stage prostate cancer can hope for better palliation of symptoms and the possibility of prolonging life.

"We're in this business to make the future better for our patients," she adds. "Everything we do adds a small step forward to hopefully solving the problem of cancer." She is very aware that progress would not be possible without the willingness of patients to volunteer for clinical trials.

"Most of the patients we deal with have metastatic cancer," says Hussain. "They are facing death, but they are very brave. While there may or may not be a benefit to them personally, they choose to go ahead with the understanding that, even if it's not to their benefit, it's to the benefit of other patients. I think that is incredibly remarkable."

What do you do when your patient with clinical depression doesn't respond to the first antidepressant you prescribe? Should you try a different drug? What about psychotherapy? How about a combination of drugs and therapy?

Surprisingly, physicians can't always answer these questions, because there are no definitive results from a clinical study comparing the effectiveness of different treatments for depression. Without scientific evidence to guide them, all doctors can do is try different options until they find one that works.

Elizabeth Young, M.D., believes there must be a better way to treat clinical depression — a debilitating condition affecting 18 to 20 million Americans — other than using trial and error. A professor of psychiatry in the medical school and senior research scientist in the U-M Mental Health Research Institute, Young is an academic scientist who seems comfortable working with graduate students in the laboratory, as well as residents in the clinic.

"Think of the impairment people suffer from depression, and realize that it takes 12 weeks to decide whether the patient is responding to medication," says Young. "That's an immense amount of time and lost productivity out of a person's life."

Though she had been principal investigator on several studies, Young had never managed a large, multi-site clinical research study before. But she agreed to direct the U-M Health System's participation in STAR*D (Sequenced Treatment Alternatives to Relieve Depression), a national study of 4,000 patients in 14 regional centers sponsored by the National Institute of Mental Health.

STAR*D is the first study to determine the most effective treatment options for the 50 percent of clinically depressed patients who do not respond to initial treatment with an antidepressant. The study began in 2001 and is now nearly finished.

Young discovered that managing a large, complex study with thousands of ➤

Maha Hussain

ELIZABETH YOUNG (SECOND FROM LEFT), WITH STAR*D TEAM MEMBERS MICHAEL KLINKMAN (M.D. 1982, RESIDENCY 1985), KATE HARRIS BULLARD AND HEDIEH BRIGGS

Young believes that the field of pharmacogenomics — where medications are selected to match each patient's genetic make-up — has great promise for the treatment of depression.

research subjects was very different from being the principal investigator on a study with 30 to 40 subjects. For one thing, she rarely saw a patient. Most of the direct contact with the 248 U-M patients enrolled in STAR*D was handled by Young's three research study coordinators and the participating study physicians.

"The study coordinators formed very strong bonds with the patients — the trial would not have functioned without the coordinators. They did all the work," Young says humbly. "I just attend meetings and strategize."

In the first years of the study, Young met weekly with her research coordinators to review the records of every patient and ensure that the complex STAR*D protocol was followed to the letter. She also had weekly conference calls with directors of the 13 other regional centers and the national coordinating center at the University of Texas-Southwestern Medical Center. Young is now helping to analyze the data and will work with other members of the study team to write articles on the results of the trial for publication in medical journals.

Monitoring and reporting adverse events is a strict requirement of every clinical trial. But when the trial involves people with depression, the stakes are especially high, because the risk of suicide in depressed patients is highest in the weeks just after treatment begins.

Most clinical trials for antidepressants are sponsored by pharmaceutical companies. They generally exclude anyone who reports thoughts of suicide, or what psychiatrists call suicidal ideation. But this was not grounds for exclusion in the STAR*D trial. Instead, Young explains, the protocol was designed with frequent patient follow-up and safeguards to protect depressed patients from acting on a suicidal impulse.

"So far in the STAR*D trial, there has not been a single suicide," Young says. "With 4,000 patients entered, that is quite amazing. The close monitoring and dedication of the staff makes a huge difference."

Since she joined the medical school faculty in 1984, Young has conducted many studies in animals and humans on the relationship between stress, depression and hormone regulation. In one of these studies, Young found that women with depression who respond abnormally to stress hormones are less likely to respond to the anti-depressant Prozac.

All the women in this study were local volunteers who answered an advertisement for study subjects. Several had no medical insurance. Young worries that they enrolled in the study because it was a way to get medical treatment they could not otherwise afford.

"For some people, clinical trials are their only source of medical treatment," Young says. "I feel good that we can help ➤

Guardians of Safety

INSTITUTIONAL REVIEW BOARDS PROTECT SUBJECTS AND RESEARCHERS — AND THE INSTITUTION ITSELF

It's twelve o'clock on Thursday afternoon as the regular crowd shuffles into a conference room near the U-M hospital cafeteria. It's mostly doctors and scientists — but also a pharmacist, a writer, a minister, an attorney and some community volunteers from the Ann Arbor area — all gathered for a weekly meeting of one of the medical school's four Institutional Review Boards, called IRBMED for short.

There's an alphabet soup of federal agencies overseeing research involving human subjects — OHRP, NIH, FDA, OCR, OBA — and they all require that IRB approval be obtained before any research study involving people can begin.

The IRB's job is to protect the safety, welfare, privacy and dignity of people who volunteer to participate in clinical research. Board members must weigh the risks of participating in the study with its potential benefits — either directly to study participants or to knowledge that can be used to help others. If the potential benefits don't outweigh the risks, the IRB has the authority to reject a research study. If the IRB votes "no," no one can overrule that decision.

Every research protocol, every adverse event, every consent document, every progress report for every clinical research study in the U-M Medical School is reviewed in detail by an IRB board member, who makes a presentation about the study to the board. Then the board votes to either approve, request revisions or reject the study. In late 2004, IRBMED had processed 4,486 submissions for 939 principal investigators and 2,934 clinical research studies.

"Our first obligation is to protect patients and other individuals who participate in clinical research," says John G. Weg, M.D., co-chair of IRBMED and a professor emeritus of internal medicine in pulmonary and critical care. "In this way, we facilitate the ability of the investigator to do research."

Weg, Ward and Hutchinson

When it comes to protecting the safety and rights of people in clinical research studies, the federal government is extremely serious. Since 1999, the Office of Human Research Protection has sanctioned six major U.S. medical centers for violating federal rules and regulations governing research with human subjects by shutting down all federally funded research at those institutions. The U-M has never had its research privileges suspended, and the people responsible for U-M's nearly $750-million research enterprise want to keep it that way.

"Serving on the IRB is a serious role with a lot of responsibility," says Raymond J. Hutchinson, M.D., a professor of pediatrics and communicable diseases and co-chair of IRBMED. "I don't think people realize the amount of time and dedication IRB members commit to the review of these protocols."

"The amount of clinical research in the medical school and the complexity of federal regulations have increased exponentially in the last 20 years," Weg says. "In 1980, the medical school had one IRB with 12 members run by one person and his secretary. Now we have four IRBs with 72 members run by a full-time director with an administrative staff of 17."

"It's a moving target, because all the agencies that supervise us are continually re-evaluating and re-interpreting their regulations," says Patricia Ward, director of IRBMED. "We try to use our expertise to efficiently and effectively help investigators conduct their research in a responsible way."

"No one is in love with regulations and they have become more restrictive than they used to be," Hutchinson says. "But once you understand the IRB's mission, you feel better about the rules."

Sally Pobojewski, Medicine at Michigan*'s science editor, is a new member of the U-M Medical School's Institutional Review Board.*

people get treatment for their depression, but there's always the concern that we are taking advantage of the uninsured. And there's the ethical dilemma of making sure people can continue on the medications after the study is over."

For these research studies, which required blood samples, Pap smears and physical exams, Young relied on the U-M's General Clinical Research Center (GCRC), which has been funded continuously by the National Center for Research Resources, part of the National Institutes of Health, since the mid-1960s. Directed by John Wiley, M.D., an associate professor of internal medicine, the GCRC provides free room-and-board and medical services for research subjects participating in U-M clinical trials, as long as the protocol is approved by the center's scientific review committee.

Although she appreciates the importance of the STAR*D trial, Young is frustrated by the lack of funding for research to discover what's different about the brains, genes and biochemistry of people with depression. "We have powerful tools like PET scans and functional MRI imaging where you can look at activated pathways in the brain — pathways that are abnormal in depression," Young says. "But not much is being done to take this imaging data into the treatment sphere and use these tools to understand more about depression."

According to Young, the last major breakthrough in the treatment of depression came in 1988 with the introduction of Prozac — the first antidepressant in the new class of SSRIs. "Although there have been incremental steps since then, we've learned a lot less than we'd like to know," she says. "Most of the newer drugs have not been very different since the first SSRI was released." Recent small-scale clinical trials of novel treatments have been discontinued because of toxicity or lack of effectiveness, she adds.

Young believes that the field of pharmacogenomics — where medications are selected to match each patient's genetic make-up — has great promise for the treatment of depression. But she says that a lack of physician-scientists trained to conduct clinical research in psychiatry, as well as what she believes is dominance of depression research funding by the pharmaceutical industry, make it unlikely that progress will come soon.

Nancy Barbas

Young holds strong views on the hotly debated funding issue, and she's not shy about sharing them. "Basically, the pharmaceutical industry is not interested in knowing the factors that tell you which drug to use," she believes, "because that only serves to lose them market share and would be an economic loss to them. They survive with big blockbuster drugs, not drugs with small niche markets."

He may not remember her name, but he knows who she is, and he's obviously delighted to see her. When Nancy Barbas (M.D. 1984) greets her patient in the waiting room of the U-M Geriatric Center's Cognitive Disorders Clinic, the 74-year-old former attorney breaks into a huge smile.

His Alzheimer's disease is progressing rapidly now, but he's still in great physical shape and proud of it. "Feel my muscle," he says. For this patient, words were the first thing to go. Now he can't even remember the names of common objects, like a paper clip or safety pin.

But sometimes his answers are surprising. "What's the name of this place?" asks Barbas, a clinical assistant professor of neurology. "U of M," he answers. "A

wonderful place where you help people get better."

Barbas' patient is accompanied by his daughter — a young woman in her 20s. Her father has been more agitated recently, and she's worried about whether it's time to move from his assisted living facility to a place where he'll have 24-hour care. Barbas suggests trying an adjustment in medication first and offers reassurance. "You're doing a great job," Barbas tells the man's daughter and encourages her to call anytime she has questions or needs advice.

in development right now that are ready to go into clinical trials."

Currently, Barbas, who joined the faculty in 1991, directs the U-M Health System's participation in two national, multi-center clinical trials funded by the National Institute of Aging (NIA). One is for an anti-seizure drug called valproic acid. The goals of this study are to see if valproic acid will delay or control the aggressive behavior that often accompanies the later stages of Alzheimer's disease, and to measure whether modification of underlying degenerative brain changes

Plus, Barbas says there are misconceptions about participating in a clinical trial. "People have a fear of being 'guinea pigs,'" she says. "Before anyone will allow us to give these drug compounds to people, they have been closely looked at from a great many angles. The safety profile is often well-known and safety monitoring is strict and ongoing."

What's less commonly known to the general public are the advantages of enrolling in a research study, Barbas adds. "Being in a clinical trial gives the patient and family a personal support

Barbas says the last 10 years of basic scientific research have led to breakthroughs in thinking about the underlying causes of plaques and tangles in the brain, which are the hallmark of Alzheimer's disease.

Barbas is a slender, petite woman with a quiet voice, who treats her Alzheimer's patients with great warmth and respect. Positive and optimistic about Alzheimer's, she is quick to correct any reference to its being hopeless or a fatal disease.

"Fatal implies it's going to kill you, but people live for 10 or more years with Alzheimer's," she says. "It's a chronic, progressive disease that, at this point in time, we have no cure for. But there's a lot we can do to delay the progression of symptoms, and the future is much more hopeful now than it has been."

Barbas says the last 10 years of basic scientific research have led to breakthroughs in thinking about the underlying causes of plaques and tangles in the brain, which are the hallmark of Alzheimer's disease.

"We know the plaques and tangles are there," Barbas says. "But how they got there, whether they were the first or last thing to appear, whether they are the cause or result, we don't know. One area of exciting new developments focuses on plaques directly — some compounds interfere with proteins that lead to plaque formation, some interfere with the protein's ability to aggregate into plaques, and still others break up plaques that have already formed. There's a multitude of new approaches

takes place. "The behaviors are terribly disturbing symptoms for family members," Barbas says. "They can lead to institutionalization, because it makes it so difficult to care for a loved one at home."

The second NIA-sponsored trial is based on the discovery that a protein called homocysteine is present in abnormally high amounts in the blood of people with Alzheimer's disease. One group of individuals in this study will receive high doses of B-vitamins and folic acid to reduce the level of homocysteine in their blood. Patients will be followed to see if the group receiving the vitamins has a slower rate of cognitive decline than the control group.

Barbas also was the principal investigator on an industry-sponsored trial for a drug called memantine, designed to slow symptom progression, which was approved by the FDA in 2003 for use in patients with Alzheimer's.

Recruiting patients for her research can be difficult, Barbas says. Learning that you have Alzheimer's disease can make it hard to think about anything else.

"The diagnosis itself is overwhelming for patients and their families," she says. "The level of commitment when you volunteer to be in a research protocol is just too much for many individuals."

system. Patients do have to come in for appointments more often, which is hard. But they also get their questions answered more frequently. They have the experts at their fingertips, and the study team is very responsive to their needs. They are also contributing to knowledge that will help in discovering new treatments for Alzheimer's disease."

She also points out that most clinical trials for new drugs being submitted for FDA approval have what's called an extension or open-label phase. As patients complete their participation in the trial, they are offered the opportunity to continue receiving the drug at no charge until the FDA makes a final decision and the drug is available for general use.

Barbas says her greatest satisfaction comes from seeing advances in clinical research lead to an improvement — small or large — in the lives of her patients. "I'm very comfortable being in the role of a physician who treats chronic disease," she says. "As doctors, we need to support people through their chronic diseases — not only in the clinical setting, but in the research setting, as well." m